Remarks

This Amendment is in response to the Office Action mailed on December 8, 2008 in which claim 44, previously indicated to be allowable if written in independent form, was said to be rejected upon further consideration as being obvious over Dudek etal (USP No. 6, 291, 516) and Beachy et al (USP No. 7, 291, 626) in view of Taipale et al (*Nature* 2000;406:1005-1009). The rejection is traversed.

Claim 44 and new claims 45 to 59 are pending in the application. Claims 45-59 are directed to subject matter previously submitted and acted upon, but cancelled without prejudice in order to expedite prosecution. In view of the withdrawal of the previous indication of allowability and impositions of new rejections of claim 44 the objective of expediting prosecution has been defeated. Therefore the previously cancelled subject matter is resubmitted here. Support is discussed in parts II and III below.

I. Claim Rejections – 35 U.S.C. § 103(a)

Claim 44 was rejected as being made obvious by Dudek et al, Beachy et al and Taipale et al. The rejection is traversed. The cited prior art do not render the presently described and claimed subject matter obvious. To the contrary, the presently claimed invention as a whole was highly unexpected in view of prior art, including Dudek et al, Beachy et al and Taipale et al taken together. The actual experimental results described in prior art as well as the wisdom in prior art were teaching away from the presently claimed invention.

A. Dudek etal's Teachings As A Whole

Dudek et al was extensively discussed and disposed of in the first round of examination. See applicant's responses dated June 24, 2005, December 2, 2005 and January 10, 2007, and also the Declaration of Dr Sinan Tas also filed January 10, 2007.

Dudek et al is an omnibus disclosure, disclosing an unlimited number of compounds ("subject compounds"; Col. 6, line 19 to Col. 13, line 15; Col. 14, line 23 to Col. 15, line 28; Col.

16, lines 31-41; Col. 27, line 21 to Col. 38, line 13) that are said to be used in a “subject method” of “modulating” cellular functions or of treating a virtually unlimited number of highly heterogenous disorders (see Col. 38, line 14 to Col. 53, line 5). “Subject method” consists of contacting cells with a subject compound *in vitro* or *in vivo* and “subject compounds” are said to be regulators of Hedgehog signaling that include both antagonists and agonists of said signaling. Not only the agonists (see Col. 15, lines 21-28) have the opposite effect of antagonists but a subgroup of subject compounds, “cAMP regulators”, are well known to have a primary effect on a huge number and variety of cellular and physiological functions. Consequently, except when a clarification is made (or can be inferred) as to the nature of “subject compound” to be used for a given condition, the disclosure is ambiguous as to which compound is to be used and what effect may be obtained. In addition, where the nature of the subject compound to be used is understood, the teaching is clearly inoperative for entire categories of the disorders said to be treated beneficially. For examples of such inoperative teachings in Dudek et al, see the paragraph bridging pages 8 and 9 in the 6.11.2007 dated amendment referring to the USP 6, 432, 970 (Beachy et al '970) which has disclosures largely similar with Dudek et al (identical word-by-word over extended passages). Therefore, a person skilled in the art must carry out an undue amount of experimentation just to determine an operative teaching apart from an inoperative teaching in Dudek et al.

The ambiguity and lack of enablement in Dudek et al is compounded by the fact that the unsupported disclosures (i.e. those that are not supported by experimental data or another evidence, e.g. by reference to findings in the scientific literature) are made commonly using unspecific verbs (uninformative in context) and/or are self-contradicting. For example, administration of a subject compound is stated to be used to “affect” (Col. 38, line 66) or “alter” (Col. 38, line 56) or “change” (Col. 17, line 30) or “control” (Col. 40, line 56) or “manage” (Col. 45, line 64) or “manipulate” (Col. 44, line 31) or “modulate” (Col. 38, line 16) or “regulate” (Col. 43, line 50) differentiation of cells. The variety and consistent use of these unspecific characterizations point out to the speculative nature of such unsupported disclosure. Similarly, concerning the expected effect of subject method on differentiation of particular cells, see Col. 48, lines 25-46 stating “*... application of a subject compound can reduce the abnormal proliferation* *and differentiation of the affected epithelium*" and see Col. 50, lines 47-49 stating "... *the subject method can be used to induce differentiation and/or inhibit proliferation of epithelially derived tissue*". Since Dudek et al consistently state that application of a Hedgehog antagonist to cells causes inhibition of their proliferation, a skilled artisan may be able to deduce from these passages that a Hedgehog antagonist is meant to be used as a subject compound. However, the skilled artisan derives self-contradicting teachings from these passages concerning the expected effect on the differentiation of epithelial cells. Likewise, see e.g. Col. 42, lines 1-4 and Col. 50, lines 20-35 making self-contradicting unsupported disclosures concerning the expected effect on cell survival/cell death. It is stated in Col. 42, lines 1-4 that "... *subject compounds can be utilized to cause such transformed cells to become either postmitotic or apoptotic*" whereas it is stated in Col. 50, lines 20-35 that "... *because a subject compound will often be cytostatic to epithelial cells, rather than cytotoxic, such agents can be used* ... (for) *preventing ... activation of cell death programs*". The skilled artisan notices, besides the self-contradiction, the generalized nature of the latter teaching and the consistent teaching of a causation of an inhibition of proliferation effect by a subject compound. The skilled artisan further notices that it is not evident from the former disclosure which of the stated alternatives will be obtained under what conditions but that a cell ceasing to proliferate will not become apoptotic or that the two effects will not be obtained in the same cell population.

It must be pointed out that, *in the absence of an actual result or evidence, unsupported expressis verbis disclosures of all potential effects, including the precise opposite effects, of a treatment in a patent application and contending that it is enabling regardless of which effect turns out to be correct is a deception that has no place in principled examination*. Skilled persons reading such disclosures filter them for what reasonably can be expected in light of their experience and the state of the art at the time the document was written. The Examiner is required by law to do the same. Picking and choosing from these possible effects in hindsight based on applicant's disclosure is impermissible reconstruction of the prior art.

As noted by the Examiner, it is true that Dudek et al teach use of a Hedgehog antagonist to inhibit abnormally high proliferation rate of tumor cells arising from activation of Hedgehog signaling and, as such, Dudek et al suggest determination of Hedgehog/Smoothened signaling in tumor cells before treatment. It is further true that, as also mentioned in the Office Action, numerous tumor types besides basal cell carcinomas (BCC's) were well known in prior art to show activation of Hedgehog signaling due to inactivating mutations of patched and/or activating mutations of smoothened and/or due to other genetic changes and the Basal Cell Nevus Syndrome (BCNS) arising from patched haploinsufficiency was known to predispose to BCC's and numerous other tumors. See e.g. the review of prior art in Dudek et al, Col. 52, lines 15-65 (see also page 1, line 30 to page 2, line 16 in the specification; the NBCCS is synonymous with BCNS). Accordingly, a skilled artisan would have been motivated to administer a Hedgehog antagonist to a patient having such a tumor with expectation of achieving inhibition of tumor cell proliferation and inhibition of tumor growth. However, as already established two years ago in the record in this case (see ¶¶21-22 of Declaration of Dr. Tas's declaration filed Jan. 10, 2007), the Office Action is clearly and definitively mistaken concerning what Dudek et al demonstrate in medulloblastoma-bearing mice and concerning the statement that an administration to inhibit tumor growth can cause the presently claimed technical effects and therapeutic results.

The *in vivo* investigations involving cyclopamine administrations to medulloblastoma-bearing mice that the Office Action refers are described in Col. 63, line 51 to Col. 64, line 16 and in Figure 3 in Dudek et al. It is described therein that medulloblastoma tumor cells were transplanted into brains of nude mice and, after allowing time for growth (5 weeks), the animals were given once-daily injections of cyclopamine (1.1 mg/kg, intraperitoneally to 3 mice) or vehicle (to 2 mice). One of the three mice in the cyclopamine-receiving group was sickened during the injections and had to be processed on day 12 of injections. The rest of the animals were sacrificed on day 14 of injections. Brains were sectioned and stained for β-galactosidase which is encoded by a transgene present only in the tumor cells and expressed under the influence of Hedgehog (Hh) signaling. Serial brain sections were examined to determine the volume occupied by the β-galactosidase expressing tumor cells. It must be pointed out that the β-galactosidase activity used to stain the brain sections detects only the tumor cells showing Hh signaling and that the tumor cells with inhibited Hh signaling are not detected by the described staining.

Results of experiments are shown in Figure 3. That figure shows that the cyclopamine-injected group tended to have smaller "relative tumor volume" in comparison to control group but the difference was not significant even though the datapoint for the animal processed earlier than others was inappropriately included in the cyclopamine-injected group (statistical significance calculated from the data set shown in Figure 3). Thus, objectively, the experiments described by Dudek et al at best suggest a possibility of inhibition of Hh signaling in tumor cells *in vivo*.

It is further clear that the treatment described by Dudek et al does not and cannot show causation of a decrease of tumor size relative to the tumor size at the start of treatment. Dudek et al 's design of the *in vivo* investigations is lacking a measurement of tumor volumes prior to the initiation of treatment, which would be a necessary prerequisite to a determination or showing of causation of decrease of size or disappearance of a tumor by the treatment. In such an investigation design the results cannot be expressed relative to the volume of tumor at the start of treatment. The "relative tumor volume" shown in Figure 3 are therefore volumes in arbitrary units where the smallest tumor is arbitrarily assigned a value and the volumes of other tumors are expressed relative to the smallest tumor. It should also be noted that the "volume" measured at the end of the treatment period is the volume occupied by the tumor cells exhibiting Hh signaling and not the actual tumor volume.

Finally, the skilled person does observe that the treatment described by Dudek et al was followed by serial sectioning of the tumors which were examined microscopically. Such examinations ordinarily do allow detection of apoptosis. A skilled person inspecting such slides would certainly have looked for this and reported it if seen. Dudek et al 's failure to report causation of apoptosis therefore is evidence that the dosage employed may have caused inhibition of Hh signaling but not apoptosis.

In conclusion, the aforementioned experiments and results described by Dudek et al demonstrate only a possibility of an inhibition of Hh signaling in tumor cells *in vivo* by administration of cyclopamine. Even when the described tumor volume measurements are considered (for the sake of argument) to reflect the actual tumor volumes at the end of treatment, it is clear that the design of experiments is suited only for a determination of the effect of cyclopamine administration on tumor growth. In accord with the design of experiments, what Dudek et al are contemplating to achieve by administration of cyclopamine is an "*inhibited tumor growth in vivo*" (Col. 64, lines 10-12).

Further reasons why Dudek et al and the other cited prior art do not meet the present claim limitations and do not make the presently claimed invention anticipated or obvious are shown below.

It must be emphasized that the present application is not claiming a mechanism of action and is not claiming technical effects and therapeutic results that were inherently present in prior art but were unrecognized. A tumor existing in a human subject cannot be caused to decrease in size or to disappear unless the tumorigenic cells are eliminated at a rate exceeding the arrival of new tumorigenic cells through proliferation and this must be achieved in a patient while keeping him or her alive. The specification of the present application shows in this respect that the presently described apoptotic elimination of tumor cells *in vivo* and the consequential therapeutic results are ***dose-dependent*** and require administration of a dose above and beyond a dose effective to inhibit proliferation of tumor cells (Appendix A attached herewith and Dr. Tas' declaration filed Jan. 10. 2007 at ¶¶ 26-29). As ready discussed repeatedly in the prosecution of this application (e.g. Dr Tas' declaration at ¶¶ 13-16) numerous post-published scientific investigations have independently confirmed that cyclopamine or another selective inhibitor of Hedgehog/Smoothened (Hh/Smo) signaling can be used to cause shrinking and disappearance of tumors *in vivo* through the apoptotic elimination of tumor cells and that said achievement requires administration of a dose that far surpasses a dose effective to inhibit proliferation of tumor cells or effective to inhibit Hh/Smo signaling. The Office's failure to make findings on these publications does not remove this objective evidence from the record.

See for example Sanchez P et al, *Mechanisms of Development* 2005;122:223-230, describing that administration of cyclopamine to medulloblastoma-bearing mice in a dose magnitudes greater than that described by Dudek et al (i.e. 10 mg/kg every other day for 30 days versus 1.1 mg/kg intraperitoneally each day for 14 days) caused inhibition of proliferation of the tumor cells along with the inhibition of Hh/Smo signaling but did not suffice to cause apoptosis of tumor cells. Sanchez et al (ibid) report that cyclopamine could be used to induce apoptosis of said tumor cells but this required greater doses. Similarly, see Berman DM et al, *Science* 2002;297:1559-1561 describing inductions of differentiation and apoptosis of medulloblastoma cells by use of cyclopamine or of a derivative thereof and describing shrinking and disappearance of medulloblastoma tumors in mice following systemic delivery of about 50 mg/kg cyclopamine each day for 24 days. The amount of cyclopamine given by this latter dosing schedule can be calculated to be more than 75 fold greater than that given by Dudek et al to medulloblastoma-bearing mice. It is also several folds greater than the dose found to be effective for inhibiting proliferation of tumor cells but found to be ineffective for their elimination by apoptosis (Sanchez et al, ibid).

A person skilled in the art treating a patient routinely administers a prior art medicament in a dose to produce a known and expected effect. In prior art Hh/Smo signaling was known to have a direct stimulatory effect on cellular proliferation and the widespread Hh/Smo signaling activation in tumors was ascribed to said stimulation of proliferation (see e.g. Barnes EA et al, *The EMBO Journal* 2001;20:2214-2223). Besides the stimulatory effect on proliferation, Hh/Smo signaling was thought to induce differentiation of tumor cells (see Nilsson M et al, *Proceedings of the National Academy of Sciences of USA* 2000;97:3438-3443). Dudek et al also teach stimulation of cellular proliferation and induction of differentiation by Hh/Smo signaling and teach causation of inhibition of proliferation and inhibition of differentiation due to inhibited Hh/Smo signaling by reference to prior art scientific publications (see Col. 3, lines 16-33, 43-50, 60-63; Col. 44, line 64 to Col. 45, line 11; Col. 49, lines 29-41). The skilled artisan who would have been motivated by the prior art to administer a selective inhibitor of Hh/Smo signaling to a tumor bearing patient with an expectation to produce an inhibition of tumor cell proliferation and inhibition of tumor growth effect is well acquainted with the limitations of prior art cancer chemotherapy arising from adverse effects on normal cells. In particular it was common knowledge that unwanted effects on normal stem cells and progenitor cells severely limit doses of prior art cancer chemotherapeutics that can be administered to a patient. Since Hh/Smo signaling was well known to be required for various normal functions of cells in adults and since normal stem cells were described to have an absolute dependence on Hh/Smo signaling (Zhang Y et al, *Nature* 2001;410:599-604), a skilled artisan would be particularly careful not to exceed a dose effective to produce a previously known and expected effect (i.e. suppressions of tumor cell proliferation and of tumor growth). However, it is clear that administration of a dose of a selective inhibitor of Hh/Smo signaling to produce inhibition of tumor cell proliferation and inhibition of tumor growth cannot produce the presently claimed effects and therapeutic results. Hence, Dudek et al neither anticipates present invention nor makes it obvious.

Further objective findings of fact that show that prior art, including Dudek et al, does not make the presently claimed invention obvious are given below.

B. Taipale et al 's Teachings As A Whole

Taipale et al describe *in vitro* treatments of transformed cells exhibiting constitutively activated Hh/Smo signaling with cyclopamine or a derivative thereof. Results of *in vitro* treatments would not necessarily be translatable to the *in vivo* situation, at least because of much greater complexity of *in vivo* environment. Taipale, like Dudek et al has already been discussed numerous times in the record of this case, including in combination with the teachings of Dudek et al (see e.g ¶ 29 of Tas declaration filed Jan 10, 2007.) However, since it is now relied upon in the outstanding Action, it is again analyzed herein whether or not it, alone or together with Dudek et al and/or Beachy et al '626, would make the presently described and claimed invention obvious.

Taipale et al refer to the prior art drug treatments of cancer and state that their cytotoxic effects on proliferating cells are to be avoided in treatment of cancer. See page 1005, left column "Current approaches to treatment of such neoplastic disorders are limited by the cytotoxic effects … Alternative mechanism-based approaches … might avoid such toxicity".

In its common meaning in art, the term "toxicity" may mean any of diverse unwanted effects in a living organism. The term cytotoxicity means toxicity on cells and the cytotoxic effects may include a cell killing effect. However, even when the term cytotoxicity is taken to mean a cell killing effect, it is well known that cell killing may result from any of various damages to cellular constituents and by a variety of means. For example, various compounds, in particular lipid soluble and cholesterol-like steroidal compounds, have long been known to cause damage to cell membranes to exert toxicity *in vitro* and/or *in vivo* and to cause membrane rupture and necrotic cell death when excessive (see e.g. Jorns A et al, *Journal of Endocrinology* 1997;155:283-293; Baker D et al, *Clinical Toxicology* 1987;25:199-208). Disruption of the cholesterol rich plasma membrane's structure and function by cholesterol-like steroidal alkaloids was known and hemolysis (lysis of erythrocytes) was utilized as a convenient assay to determine and predict cell lysis by naturally occurring and synthetic steroidal compounds (see e.g. Takechi A et al, *Phytochemistry* 1996;41:121-123 and see Zhang J et al, *Clinica Chimica Acta* 1999;289:79-88 describing isolation of such alkaloids from a plant belonging to *Liliaceae*, the plant family that includes the *Veratrum*). Authors of the Taipale et al publication were also aware that cyclopamine and other cholesterol-like steroidal alkaloids have a disruptive effect on plasma membrane, on cholesterol esterification and cholesterol transport through cell membranes (see reference 3 in Taipale et al publication which has the same corresponding author as Taipale et al and see Beachy et al'626, Col. 61, lines 7-8; Table 1; Col. 63, lines 57-67). In any case, what a skilled artisan derives from Taipale et al is that, when using cyclopamine, ***a cytotoxic effect is to be avoided in treatment of cancer***. In accord, Taipale et al describe experimental results where they show uses of cyclopamine and of a derivative thereof to cause abolished Hedgehog signaling (see page 1007, Figure 3a) and maximal inhibition of cell proliferation (see Figures 3c and 3d and the plateau effect at the highest doses) and state that said treatment ***did not cause cytotoxicity*** (see the legend of Figure 3). In further accord, Taipale et al declare that the described treatment which "*block ... the Hh response pathway and abnormal cell growth*" is a potential mechanism-based treatment of tumors (see page 1005, the paragraph in bold summarizing conclusions of the investigation).

Thus, the teaching a skilled artisan derives from Taipale et al is that cyclopamine or a derivative thereof can be used to block activation of Hh response pathway and abnormal proliferation of transformed cells and that said treatment will not exert cytotoxicity and that causation of cytotoxicity is to be avoided in treatment of tumors. Hence, Taipale et al taken alone or together with other prior art *does not* make obvious use of cyclopamine to induce apoptosis of tumor cells let alone achievement of said effect in tumor-bearing patients in a selective and efficient manner to achieve the described shrinking and disappearance of tumors. Induction of apoptosis in a non-genotoxic, selective and efficient manner as described in the specification has distinct advantages in tumor treatment and said effect is essential for the causation of described therapeutic results.

It must also be noted that apoptosis is a particular form of cell death and causation of it is advantageous over other forms of cell death, e.g. necrotic cell death which results in extensive inflammation (Willingham MC, *The Journal of Histochemistry and Cytochemistry* 1999;47:1101-1109). Thus, when Taipale et al teaches that the treatment was not cytotoxic, ***this is an express teaching that apoptosis was not caused***. Taipale et al provides additional objective evidence that dosages that are effective to inhibit proliferation, but that do not cause apoptosis exist and were the target of the skilled person before the applicant's invention. Contrary to the assertion in the Office Action, "the mechanism-based" treatment that Taipale et al is describing, by express teaching, is one that that is not cytotoxic.

As a consequence, the skilled person taking the combined teachings of Dudek et al and Taipale et al is specifically ***lead away*** from contemplating to administer a dosage to cause cell death. Therefore the combination clearly does not render the presently described and claimed induction of apoptosis of tumor cells in a tumor-bearing patient obvious.

C. Beachy et al '626 Teachings As A Whole

The Beachy et al patent cited in the Office Action (USP No. 7, 291, 626) (Beachy et al '626) has mostly the same disclosure with the Beachy et al patent USP No. 6, 432, 970 (Beachy et al '970) cited in the April 19,2007 and November 21, 2007 Office Actions. There is some description of additional experimental results in columns 69-78 and in Figures 8-15, but as it is discussed below these additional results lead a skilled person directly away from the presently claimed invention. Beachy '626 also has largely similar or identical disclosure with Dudek et al patent USP No. 6, 291, 516 (identical word-by-word over extended passages). No non-cumulative teachings are identified in the Office Action as the basis for citing this document so on its face the rejection appears to serve to increase applicant's prosecution time and expense.

Since the disclosure of Beachy et al '970 has been analyzed in the June 11, 2007 and Feb. 20, 2008 Amendments, reference is made to said analyses. Reference is made also to the analysis of Dudek et al above (item I.A) concerning disclosures identical between Dudek et al and Beachy et al '626. In addition, it must be pointed out that Beachy et al '626, like Beachy '970 before it ***does not have even a single case*** of description or example of treatment of any one of the virtually unlimited number of highly heterogenous maladies enlisted therein as being treatable by the "subject method" (see cols 35-47). In this respect, both Beachy '970 and Beachy '626 are even less suggestive of the present invention than Dudek et al. Nothing in the passages from columns 10 and 46 cited in the Office Action avoids the fact that these have been selected in hindsight from many similar passages pertaining to other diseases that reportedly are treatable by administration of an "effective amount" of a steroidal alkaloid according to "the subject method." Furthermore, the actual experimental results described therein teach directly away from the presently claimed subject matter as already explained in the June 11, 2007 and Feb. 20, 2008 Amendments. A more recent prior art patent application naming Beachy PA as inventor is the international patent application WO 01/27135. Said publication also does not make the presently claimed invention obvious and rather leads away (see Appendix B).

Relative to Beachy et al '970, the additional experimental results found in Beachy et al '626 describe biological consequences of a genetic elimination of Shh signaling in skin *in vivo* besides a description of the inhibition of Hh/Smo signaling in ptc -/- cells *in vitro* by treatment with cyclopamine. Beachy et al '626 describe experimental results and explicitly teach that epidermal cells as well as the epithelial cells of hair follicles proceed to differentiate to terminally differentiated cells *in vivo* regardless of the presence or elimination of Shh signaling (see Col. 72, lines 33-35; Col. 72, lines 51-55; see also Col. 69, lines 21-24). Similarly, skin tissue explants are described to express hair-specific transcripts regardless of being treated or not treated with cyclopamine and, further, epidermal differentiation is also stated not to be affected by treatment with cyclopamine (see Col. 73, lines 46-54; see also Col. 69, lines 21-24). Therefore, Beachy et al '626 leads a person skilled in the art directly ***away*** from contemplating to use cyclopamine or another selective inhibitor of Hh/Smo signaling to induce differentiation of epiderm/hair follicle lineage cells *in vivo* (It must be pointed out that Beachy et al '626 teaches also away from the related invention described by the Applicant in the parallel US patent application (10/682662) since it describes in Col. 73, lines 2-6 and in Figure 10C that the elimination of Shh signaling caused "*a thickened epidermis with focal areas of hyperkeratosis*" *in vivo* and since said feature was well known in prior art to be a characteristic of the psoriatic lesional skin).

The other new experimental results in Beachy et al '626, i.e. relating to the inhibition of Hh/Smo signaling in ptc -/- cells *in vitro* (Col. 77, line 16 to Col. 78, line 7), refer to a method of assaying Hh/Smo signaling in said cells by measuring β- galactosidase activity. Using said assay, Beachy et al describe that an inhibition of Hh/Smo signaling effect can be obtained by treatment with cyclopamine without necessarily causing an inhibition of proliferation effect in cells having ptc loss-of-function (Col. 77, line 66 to Col. 78, line 3). It is stated further that a treatment of ptc -/- cells with cyclopamine producing inhibition of Hh/Smo signaling did not exert cytotoxicity on the treated cells (Col. 77, lines 62-66). This latter description of Beachy et al'626 is in accord with the similar statement in Taipale et al which has been described above. Thus, Beachy et al'626 leads nowhere in the direction of the claimed invention and rather leads away.

While arguing that Beachy et al '626 viewed together with Taipale et al makes the presently claimed invention obvious, the Examiner has referred to Col. 12, lines 22-29 of Beachy et al '626 which states that "An effective amount of … a hedgehog antagonist … refers to an amount … which … brings about *a change* in the rate of cell proliferation and/or the state of differentiation of a cell and/or rate of survival of a cell" (emphasis added). For the same argument, Examiner has referred also to Col. 48, lines 54-61 wherein it is stated that doses of the compounds of the invention range from 0.0001 to 100 mg/kg body weight per day. The reason why said disclosures (which exist also in Beachy et al '970 and in Dudek et al) do not make the presently claimed invention anticipated or obvious had been explained in the Amendment filed

Feb. 20, 2008 in this application (see item I.C.1 and item I.A). In addition, the Applicant points out that, in the absence of an actual result or evidence, unsupported disclosures of all potential effects of a treatment in a patent application and disclosing further that a treatment will bring about "*a change*" in cellular functions and contending that it is enabling regardless of which "*change*" turns out to be true is a deception in disclosure. This sort of deception is not intended to be allowed by the law and principles of patenting which aim to promote the scientific and technological progression by encouraging research and development that bring to the benefit of human kind previously unknown and unobvious inventions. It has no place in the law of obviousness. All obviousness analyses are required to be filtered through the eyes of a skilled person reading the disclosure prior to the applicant's invention, as has been done in all of the applicant's responses to date. Obviousness analysis from the hindsight perspective displayed in the Office Action that simply ignores everything in the applied documents and the prior art as a whole is inconsistent with the contentions asserted to reject the claims.

With regard to the disclosure of Beachy et al '626 in Col. 48, lines 54-61, the Applicant points out further to the following pertaining facts, besides referring to the item I.A in the Feb. 20, 2008 dated amendment.

(i) Beachy et al '626, like Dudek et al and Beachy et al '970, disclose an unlimited number of compounds as "subject compounds" and a dose range covering a million-fold difference between the lowest and highest ends. As explained above (see "Dudek et al 's Teachings As A Whole"), it has been described by independent scientific publications that in the example of cyclopamine administered systemically, a dose falling in the first 100 000 fold subrange of said dose range would not produce the presently claimed effects and only a dose in the extreme end may be effective. Thus, a skilled artisan, in the absence of another guidance has much less than 1 in 10,000 probability of observing a presently claimed effect (100,000 /10 = 10,000). However, Beachy et al '626 (like Beachy et al '970 and Dudek et al, see 2.20.2008 dated amendment, and Tas declaration filed 1/10/2007 at ¶23) teaches to administer the lowest dose effective to produce a therapeutic effect and the described and expected therapeutic effect in prior art was the causation of inhibition of tumor cell proliferation for inhibition of tumor growth.

Administering a medicament to a patient in a dose effective to produce a known and expected effect and not exceeding the lowest dose effective is, in any case, what a skilled artisan routinely does. It must also be pointed out that any occurrence having a probability of less than 1 in 10,000 is, by definition, unobvious.

(ii) The specification in the present application shows and teaches that duration of administration of the medicament is important in obtaining described therapeutic results (see e.g. page 12, lines 5-10; page 17, lines 21-24). A person skilled in the art knows further that the term dosing schedule (page 11, line 11) entails also the duration of administration of a medicament to a patient. Numerous post-published scientific investigations have independently confirmed that, besides the amount of medicament given per day, the duration of administration is also important in obtaining a therapeutic result described in this application (see further below). The disclosure of Beachy et al '626 in Col. 48, lines 54-61 does not mention how long an administration of a subject compound will be continued except that the skilled artisan notes that the administration will be the lowest dose that will produce a known or expected effect.

The combination of Beachy'626 with Taipale et al suffers all of the deficiencies already discussed for the combination of Dudek et al with Taipale et al. As discussed for the combination of Dudek et al with Taipale et al, the combination of Beachy'626 with Taipale et al does not make the presently described and claimed subject matter obvious and rather teaches away from the present invention.

Further reasons why the Examiner is incorrect in his finding of prima facie obviousness are given below.

D. Further Reasons That Prior Art Does Not Make the Presently Claimed Invention Anticipated Or Obvious

In prior art, already starting with the cloning and identification of Sonic hedgehog in 1993, Hh/Smo signaling was known to stimulate proliferation of various cell types and the cells proliferating under the influence of Hh/Smo signaling were described to show inhibition of proliferation when treated with a compound that selectively inhibits Hh/Smo signaling (see e.g. Goodrich LV et al, *Neuron* 1998;21:1243-1257 reviewing the findings in 1998). However, causation of an inhibition of proliferation effect on cells neither anticipates induction of differentiation nor anticipates apoptosis of the same cells nor does it make causations of said effects obvious. To the contrary, it is well known that differentiation of many cell types absolutely requires proliferation for one or more cell cycles. In accord, Ericson J et al, *Cell* 1996;87:661-673 had described in prior art that inhibiting proliferation of neural precursor cells by treatment with a selective inhibitor of Hh/Smo signaling caused *inhibition* of their differentiation. In further accord, Fujita E et al, *Biochemical and Biophysical Research Communications* 1997;238:658-664 had described causation of a dose-dependent inhibition of proliferation of human lung cancer cells by treatment with a selective inhibitor of Hh/Smo signaling but no induction of differentiation or apoptosis was described even though the proliferation-inhibited tumor cells were examined by microscopy which ordinarily allows detection of said effect when caused. Said prior art, pre-dating the earliest priority date of the Dudek et al and Beachy et al '626 patents cited in the Office Action show that the presently claimed effects are not anticipated and are not made obvious by the inhibition of proliferation and inhibition of Hh/Smo signaling effects described in said patents. Errors in the allowance of the cited patents are also implied by said prior art particularly since cyclopamine was described to inhibit Shh signal transduction prior to the earliest priority dates of said patents (see Coventry S et al, *Pediatric and Developmental Pathology* 1998;1:29-41).

Besides the aforementioned reasons and the reasons given in analyses of Dudek et al, Taipale et al and Beachy et al, there are numerous findings of fact which objectively show that the presently claimed invention was unobvious in view of entire prior art (see the 2.20.2008 dated amendment, pages 28-36, items I.D, I.F). In particular, it must be pointed out that damaging of the normal stem cells and progenitor cells of patients by the non-surgical cancer treatments were well known in prior art to severely limit their applicability and utility. Anemia and loss of hair are just some of the externally visible signs of such damaging that are nearly universal in cancer patients receiving prior art chemotherapy. Yet normal stem cells were described in prior art to have an absolute dependence on Hh/Smo signaling (Zhang Y et al, *Nature* 2001;410:599-604). Prior art had concluded further that induction of apoptosis of tumor cells in a patient to eliminate an existing tumor while sparing normal cells is an unattainable goal on theoretical grounds and in consideration of the vast clinical experience (reviewed in Hannun YA, *Blood* 1997;89:1845-1853). Ber-Ep4 immunostaining used in the specification in demonstration of the sparing of undifferentiated cells in the normal skin tissue exposed to the same dose of medicament as tumor cells was known to detect the normal epithelial cells having stem cell and progenitor cells features (see e.g. the references in Appendix A). The presently claimed invention was clearly against the wisdom and prejudices in prior art.

The presently claimed invention was unpredictable and unexpected in prior art also due to the nature of Hh/Smo signaling. Even non-inclusive screening assays have revealed hundreds of genes as targets of Hh/Smo signaling (see Xu J et al, *Genetics* 2006;174:735-752; DasGupta R et al, *Genome Biology* 2007;8:R203). The Ci/Gli family proteins (Gli1, Gli2, Gli3 in vertebrates) are the nuclear executors and sole end point of Hh/Smo signaling and can act as transcriptional activator or repressor of target genes of Hh/Smo signaling depending on their proteolytic processing in proportion to the arrival of a Hh protein to the cell (Xu et al, ibid; Wang QT et al, *Development* 2000;127:3131-3139; Methot N et al, *Development* 2001;128:733-742; Bai CB et al, *Developmental Cell* 2004;6:103-115). Which particular sets of Hh target genes will be expressed in a cell is found to depend not only on the arrival of a Hh protein to the cell but also on how much Hh arrives for how long and on the cell type and previous exposures of a cell since a Hh target gene to which a Ci/Gli family protein binds often has additional regulatory elements (Xu et al, *ibid*; Wang et al, *ibid*; Methot et al, *ibid*; Stamataki D et al, *Genes & Development* 2005;19:626-641). Therefore, a priori, a huge variety of potential responses exist to the administration of an inhibitor of Hh/Smo signaling to an organism and there was no teaching in prior art that would make the presently claimed particular effects and therapeutic outcome expected or predicted. To the contrary, prior art as a whole was teaching away from the presently claimed invention as explained above and in the 2.20.2008 dated amendment.

The record in this case, including specifically the teachings of Taipale et al, establishes that the claims are directed to a result that can be achieved only in a part of the dosage range disclosed in Beachy '626 when administered to the tumors described in Beachy '626. The prior art does not provide any specific motivation to formulate to these dosages and in fact provides specific reason and suggestion not to. See discussion of Taipale et al above. Prima facie obviousness has not been shown. See *Ex parte THOMAS J. WHALEN II,* ---USPQ2d ___ (USPTO Board of Patent Appeals and Interferences 2008) a precedential decision binding on the Examiner, available at: `http://www.uspto.gov/web/offices/dcom/bpai/prec/fd074423.pdf`.

II. Support For the Claimed Subject Matter In the Originally Filed Application

This application incorporates the international applications PCT/TR01/00027 and PCT/TR02/00017 by reference in their entirety. Cyclopamine is stated to be a teratogenic Veratrum alkaloid that inhibits Hedgehog/Smoothened (Hh/Smo) signaling in said applications and in the present application (PCT/TR01/00027, page 2, lines 18-21; PCT/TR02/00017, page 2, line 34 to page 3, line 12; present application, page 2, line 20 to page 3, line 6; page 9, lines 14-15).

In prior art, Incardona JP et al, *Development* 1998;125:3553-3562 and Cooper MK et al, *Science* 1998;280:1603-1607 (cited in the present application on page 3, lines 4-6 and in PCT/TR02/00017 on page 3, lines 1-12) had described experimental results to conclude that cyclopamine and another teratogenic Veratrum alkaloid (jervine) inhibit Hh/Smo signaling to exert teratogenicity. Both showed that cyclopamine and jervine selectively inhibit the differentiation events induced by the Sonic hedgehog (Shh) protein in the developing brain to produce cyclopia and other features of holoprosencephaly. They showed selective action of cyclopamine and jervine on Shh signal transduction by several criteria, including quantitative results and a lack of effect on other differentiation events, e.g. due to Bmp signaling (see Incardona et al, *ibid*, page 3557, left column paragraph 3 to right column, paragraph 1; Cooper et al, *ibid*, page 1606, left column, paragraph 2 and Figure 4). The particular Shh-induced differentiation events selectively inhibited by cyclopamine and jervine were shown previously to be inhibited also by genetic elimination of Shh expression (Krauss S et al, *Cell* 1993;75:1431-1444; Chiang C et al, *Nature* 1996;383:407-413). Further, precisely the same Shh-induced differentiation events inhibited in the developing brain by cyclopamine and by a genetic loss of

Shh expression were shown to be selectively inhibited also by function-blocking monoclonal and affinity-purified anti-Shh antibodies (Ericson J et al, *Cell* 1996;87:661-673; see page 662, left column, paragraphs 2 and 3 for proof of selectivity). Hence, it was common knowledge in prior art that cyclopamine or a structurally related compound (jervine) or structurally unrelated compounds (monoclonal and affinity purified anti-Shh antibodies) can be used to inhibit Hh/Smo signaling selectively. The review article cited on page 3, lines 4-7 in PCT/TR02/00017 (Goodrich LV et al, *Neuron* 1998;21:1243-1257) also refers to said uses of cyclopamine, jervine and of function-blocking anti-Shh antibodies and describes further effective uses of latter compounds *in vivo* (see page 1252, left column, paragraph 3). Thus, the sate of the art at the time of the application was such that a person of ordinary skill in the art knew that cyclopamine as well as structurally related and unrelated other compounds can be used to selectively inhibit Hh/Smo signaling *in vitro* or *in vivo* and the scientific publications referred in the specification describe such uses.

Other compounds structurally unrelated to cyclopamine were also used in prior art for selective inhibition of Hh/Smo signaling *in vivo* (Nasevicius A et al, *Nature Genetics* 2000;26:216-220; Treier M et al, *Development* 2001;128:377-386).

Binding of a Hh protein to the receptor Patched was known in prior art to relieve the inhibitory action of Patched on Smoothened (Smo) and the relieved Smo was known to initiate signaling (see page 1, line 30 to page 2, line 16 of specification). Smo was known to be obligatory for signaling and furthermore it was unambiguously demonstrated that Hh/Smo signal transduction has a single end point, the Ci/Gli proteins that serve as transcriptional activator or repressor of Hh target genes depending on their phosphorylation-dependent proteolytic processing (Methot N et al, *Development* 2001;128:733-742). The converse was also investigated and it was found that activities of Ci/Gli proteins can be affected by non-Hh/Smo signals as well (Methot et al, *ibid*). The findings that two kinases, protein kinase A (PKA) and glycogen synthase kinase 3β (GSK3β), both negatively regulate the Ci/Gli transcriptional activator function (see e.g. Wang QT et al, *Development* 2000;127:3131-3139 and Motzny CK et al, *Mechanisms of Development* 1995;52:132-150) and that both of these kinases have multiple substrate proteins had provided an explanation for the effects of non-Hh/Smo signals on Ci/Gli proteins. Thus, several different mitogenic signals were found to act on GSK3β to downregulate it and to relieve the GSK3β substrate proteins from GSK3β mediated phosphorylation and proteolysis (see e.g. Diehl AJ et al, *Genes & Development* 1998;12:3499-3511). Since the substrates of GSK3β included cyclin D1 and β-catenin (which is required for Wnt/β-catenin signaling), it was clear that this kinase could regulate responses to multiple mitogenic signals (Diehl et al, *ibid*). Similarly, it was well recognized that whereas phosphorylation of Ci/Gli proteins by PKA promotes their proteolytic processing to inhibit transcription of Hh target genes, upregulated PKA phosphorylates many other proteins as well and PKA certainly lacks a selective action on Hh/Smo signaling (see e.g. Wang et al, *ibid*). Thus, it was clear in prior art that a single obligatory transducer (Smo) and a single end point (Ci/Gli) make Hh/Smo signaling highly suited to selective inhibition (or stimulation) by targeting Smo or a further upstream element but PKA or GSK3β would not be suitable. Several *in vitro* methods of assaying Hh/Smo signaling and the activities of individual proteins of Hh/Smo signaling were common knowledge in prior art and, furthermore, mutant mice reproducibly developing tumors showing Hh/Smo signaling overactivity were available for testing compounds identified by *in vitro* screening assays. Therefore, a person of ordinary skill in art could identify further compounds suited for selective inhibition of Hh/Smo signaling by routine testing. In addition, the skilled artisan knew numerous non-cyclopamine compounds, both structurally related and unrelated to cyclopamine, that were *already* available and shown to selectively inhibit Hh/Smo signaling *in vitro* and/or *in vivo*.

The originally filed application states directly and unambiguously that the described treatment is for those tumors "*that utilize the hedgehog/smoothened pathway … for prevention of apoptosis and/or differentiation*" of tumor cells (see page 15, lines 19-24; see also page 3, lines 24-28; page 4, lines 12-16). When presented with this definition, nature of a compound that can be used to carry out the described treatment becomes fully evident to a person skilled in the art, namely a pharmaceutically acceptable compound that will inhibit Hh/Smo signaling with selectivity so that the described apoptotic elimination of tumor cells and therapeutic results can be achieved. Further, exemplifications of the invention with actual treatments of human tumors *in vivo* show that administration of a previously well known selective inhibitor of Hh/Smo signaling (cyclopamine) in a sufficient dose induces a selective and massive apoptosis of tumor cells to cause rapid regression and disappearance of treated tumors. A skilled artisan presented with said definition and exemplifications has no uncertainity concerning the unifying functional feature of the compounds that are suitable to carry out the invention and, given the state of the art at the time of application, the skilled artisan could readily determine members of the genus of the functionally defined compounds without having to execute hit or miss testing.

The paragraph on page 10, lines 8-26 of specification states that compounds other than the cyclopamine used for the exemplification of invention can be derived from cyclopamine or synthesized de novo in such a way that they exert the described biological and therapeutic effects of cyclopamine. Said paragraph does not state that compounds structurally unrelated to cyclopamine are unsuitable to carry out the invention. Rather from the specification as a whole the skilled artisan understands clearly that compounds structurally unrelated to cyclopamine are also suitable. Since it is known that a pharmaceutically active compound may physically interact with multiple cellular constituents with varying low affinity not amounting to a physiologically relevant or detectable effect, the presently amended claims refer to a selective inhibition of Hh/Smo signaling. This is also due to the fact that the cyclopamine effect on cholesterol metabolism observed in prior art was not relevant to the inhibition of Hh/Smo signaling by it (see Incardona JP et al, *Development* 1998;125:3553-3562, page 3559, left column, paragraph 2; Cooper MK et al, *Science* 1998;280:1603-1607, page 1606, middle column, paragraph 2). It must also be pointed out that, unlike the situation in prior art, numerous post-published investigations have independently confirmed that the presently claimed technical effects and therapeutic results can be obtained in tumor-bearing subjects not only by use of cyclopamine or a derivative thereof but also by use of structurally unrelated compounds that also inhibit Hh/Smo signaling selectively. See in particular Hutchin ME et al (*Genes & Development* 2005;19:214-223) who have described a genetic means of selectively inhibiting Hh/Smo signaling in epidermal lineage tumor cells *in vivo*. These authors also confirm that a selective inhibitor of Hh/Smo signaling can be applied to tumor cells to cause their differentiation and apoptosis. Since the method used by Hutchin et al is a generic genetic means that inhibits Hh/Smo signaling selectively, it is clear independent confirmation that any pharmaceutically acceptable compound that will selectively inhibit said signal transduction can be used to achieve the presently claimed effects and therapeutic results when administered in a sufficient dose.

The originally filed application has abundant support for the dose limitation in claims as explained in Appendix A. Reference is made herein also to the previously filed amendments concerning the support for the presently claimed subject matter in the originally filed application.

III. Amended and New Claims

Claim 44 is amended to replace the word “quantity” with “dose” in view of the fact that the term dose reflects the nature of administration more accurately than the word quantity. Specific support for said amendment can be found throughout the specification (see Appendix A).

Independent claim 47 differs from independent claim 45 in that the treatment is recited to induce differentiation and apoptosis of the tumor cells. Independent claim 58 describes a medicament. As explained above, the originally filed application has abundant support for these new claims.

In the independent medicament claim 58 an "instruction" recitation has been added. Instructions are implicit for all medicaments. The application provides sufficient instruction to meet the specifics recited in claim 58.

IV. Comments on "Reasons for Reopening Prosecution"

In the statement of "reasons" for reopening prosecution it is asserted that the Applicant's have merely "identified the mechanism of action of cyclopamine" and that such does not render the invention of claim 44 patentable. This is a completely bizarre statement. It reflects a complete disregard of the actual prosecution record of this application. Repeatedly, in the past and again below, the applicant has demonstrated that apoptosis only occurs at high dosages that the prior art did not recognize and that explicit teachings in Taipale et al lead the skilled person away from. The "mechanism of action" contention is completely specious.

The citation of *In Re Bilski*, 88 USPQ2d 1385*,* in the statement of reasons for reopening prosecution is likewise completely specious. *Bilski* is a case under 35 USC §101, pertaining to patentable subject matter. No rejection under §101 has been made and none can conceivably be made under the rationale of *Bilski*. Claim 44 recites a diagnostic step that involves classification of a tumor as one suitable for the inventive treatment and a treatment step that itself is non-obvious. Nothing about the combination of these steps raises any issue under *Bilski*. *Bilski* provides not even a scintilla of a rationale for reopening prosecution.

The stated "reasons" for reopening prosecution also does not address why the rejections could not have been imposed earlier or even how, or even whether, the Examiner considers the new rejections to be non-cumulative. This was already a problem objected to when the Examiner previously switched from rejections based on Dudek et al to Beachy et al '970. See Amendment filed June 11, 2007, page 7. Now switching back to Dudek without explanation, and without even commenting on the fact that the combined teachinge of Dudek et al and Taipale et al have already been specifically discussed in the record (see e.g. Tas declaration filed Jan 10, 2007 ¶29), is arbitrary, capricious, and violates due process. Similarly the addition of the new Beachy '626 reference which has no identified teaching that is asserted to be in any way more pertinent to the obviousness of the invention of claim 44 than Dudek et al or Beachy '970 is arbitrary, capricious and violates due process.

Since there has been a previous objection to the arbitrary switching from Dudek et al to Beachy '970, and those objections were never even acknowledged much less addressed; and since there is now also a common similar practice of reopening prosecution after appeals are taken; and since the invention itself offers very substantial benefits both to the inventor and the public at large, which benefits are right now being lost because of the circular prosecution that the application has been subjected to in this case, the applicant is concurrently filing a petition for supervision to bar such arbitrary actions for the remaining prosecution of this application.

V. Conclusion

At least for the reasons given above, the presently claimed invention is unanticipated and unobvious in view of prior art. The presently amended claims, describing causations of previously unknown and unexpected technical effects and therapeutic results, define patentable subject matter. It is clear that the presently described and claimed invention has brought a highly desirable solution to the long-standing problems in prior art in treatment of cancer. Early and favorable action thereon is requested.

Respectfully submitted,
VIDAS, ARRETT & STEINKRAUS

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By: /Walter J. Steinkraus/
Walter J. Steinkraus
Registration No.: 29592

6640 Shady Oak Dr., Suite 400
Eden Prairie, MN 55344-7834
Telephone: (952) 563-3000
Facsimile: (952) 563-3001

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Appendix A: Teachings In the Originally Filed Specification Showing That the Presently Claimed Effects and Therapeutic Results Are Dose-Dependent

Appendix B: Teachings Of WO 01/27135 As A Whole and Obviousness/Unobviousness Analysis Of the Presently Claimed Invention In View Of WO 01/27135